

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION

OPIATE LITIGATION

This document relates to:

Track One Cases

MDL 2804

Case No. 17-md-2804

Hon. Dan Aaron Polster

**PLAINTIFFS' MEMORANDUM IN OPPOSITION TO DEFENDANTS'
MOTION TO EXCLUDE "GATEWAY" OPINIONS OF DRS. LEMBKE,
GRUBER AND KEYES**

July 31, 2019

In re National Prescription Opiate Litigation: MDL 2804

Summary Sheet of Concise Issues Raised

Opposition Name: Plaintiffs' Memorandum of Law in Opposition to Defendants' Motion to Exclude "Gateway" Opinions of Drs. Lembke, Gruber and Keyes

Opposing Parties: Plaintiffs Summit County and Cuyahoga County

Issue #1. Are the opinions of Drs. Lembke and Keyes, that prescription opioids are a gateway to misuse of, and addiction to, both prescription opioids and illicit drugs admissible under *Daubert* and Fed. R. Evid. 702?

Answer. Yes. Defendants argue that there is no scientific evidence of a causal link between "properly prescribed pain patients" and illicit drug use, and characterize this effect as a "hypothesis" without support. These arguments are based on a misleading and selective review of the scientific literature and Plaintiffs' expert reports, omitting sources that contradict the defense position. In fact, the Gateway Effect has been widely accepted in the scientific literature, and the progression from medical use to non-medical use to illicit drug use has also been well-documented. Drs. Lembke and Keyes relied on a substantial body of scientific evidence in reaching their conclusions, including an authoritative report of the National Academy of Science, Engineering and Medicine and numerous peer-reviewed scientific studies. The review of scientific literature is a sound methodology. *In re Gadolinium-Based Contrast Agents Products Liab. Litig.*, No. 1:08 GD 50000, 2010 WL 1796334, *mod. on recon.*, 2010 WL 5173568, *aff'd sub nom. Decker v. GE Healthcare Inc.*, 770 F.3d 378 (6th Cir. 2014) (finding expert testimony based on review of scientific literature admissible); *see also, In re Heparin Prods. Liab. Litig.*, 803 F. Supp. 2d 712738 (N.D. Ohio 2011) ("Courts have admitted expert testimony as reliable where experts extrapolate their opinions from their knowledge and experience combined with a review of the relevant scientific literature.") Plaintiffs' experts followed reliable methodologies to offer admissible opinions that both medical and non-medical exposure to Defendants' prescription opioids caused increased use of heroin and fentanyl. Dr. Lembke's and Dr. Keyes' pre-litigation publications of their findings, which match their opinions in this case, provide further assurance of the reliability of their opinions. *See Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 434 (6th Cir. 2007) ("That an expert testifies based on research he has conducted independent of the litigation provides important, objective proof that the research comports with the dictates of good science").

Issue #2: Are the opinions of Dr. Gruber, that shipments of prescription opioids caused illicit-opioid related harms, admissible under *Daubert* and Fed. R. Evid. 702?

Answer. Yes. Professor Gruber, a renowned MIT professor, applied well-recognized methods in his field of health economics, including analyses showing a close and causal relationship between the extent of shipments of prescription opioids to geographic areas and the extent of illicit opioid-related harms, including mortality. Professor Gruber's methodology included regression analyses to consider and rule out alternative causes for the higher mortality observed in areas with higher shipments of prescription opioids. Defendants' arguments are based on selective deposition excerpts that ignore Professor Gruber's actual opinions. Plaintiffs respectfully direct the Court's attention to their Opposition to Defendants' *Daubert* Motion to Exclude the Opinions Offered by Jonathan Gruber, for further exposition of the reliability of his methods and admissibility of his opinions.

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INTRODUCTION

Defendants move to exclude opinions of Plaintiffs' experts Anna Lembke, Katherine Keyes, and Jonathan Gruber that prescription opioids provide a "gateway" to heroin and fentanyl.¹ Ignoring the vast body of evidence that supports this effect (including pre-litigation publications by Plaintiffs' experts, authoritative governmental reports, and peer-reviewed literature), Defendants argue that there is no scientific evidence of a causal link between "properly prescribed pain patients" and illicit drug use, and characterize this effect as a "hypothesis" without support. These arguments are based on a misleading and selective review of the scientific literature and Plaintiffs' expert reports, omitting any and all sources that contradict the defense position. In fact, the Gateway Effect has been widely accepted in the scientific literature, and the progression from medical use to non-medical use to illicit drug use has also been well-documented. The motion should be denied in its entirety, because Plaintiffs' experts followed reliable methodologies to offer admissible opinions that both medical and non-medical exposure to Defendants' prescription opioids caused increased use of heroin and fentanyl.

Drs. Lembke, Keyes, and Gruber reached mutually supportive and reinforcing conclusions about the role of prescription drugs in the epidemic of both licit and illicit opioids, from different but compatible perspectives. Dr. Lembke, an addiction medicine specialist at Stanford, and Dr. Keyes, a professor of epidemiology at Columbia, bring their knowledge and expertise in addiction medicine and epidemiology, to assess the scientific literature linking prescription drug abuse with subsequent use of illicit opioids. Notably, both Dr. Lembke and Dr. Keyes had researched and published their views regarding the Gateway Effect long before they were engaged as litigation

¹ This motion concerns only the opinions of Drs. Lembke, Keyes, and Gruber on this topic. Defendants have separately moved to exclude the all of Dr. Gruber's opinions. They have also moved to exclude certain opinions of Dr. Lembke and Dr. Keyes (along with opinions of another of Plaintiffs' experts, Dr. Schumacher) which pertain to the falsity of Defendants' marketing. Finally, Defendants also seek to exclude portions of Dr. Keyes' opinions that relate to abatement. In this memorandum, Plaintiffs address only the challenges to the opinions of Drs. Lembke, Keyes, and Gruber that relate to the Gateway Effect.

experts; such pre-litigation work is a strong indicator of reliability. Professor Gruber, a professor of economics at M.I.T., has extensive experience in causal analysis in the field of Health Economics. He applied standard methods of statistical analysis to confirm the cause-and-effect relationship between the supply of prescription opioids and the extent of mortality related to prescription opioids and illicit heroin/fentanyl. Dr. Gruber's focus on increased shipments is analogous to Drs. Lembke and Keyes' emphasis on increased exposure, dose-response, and the chemical and experiential similarities between prescription opioids and heroin/fentanyl that make the licit and illicit drugs interchangeable from the users' perspective. Each expert followed a reliable methodology by considering the available peer-reviewed literature in their respective fields, and applying the literature to the facts of the case, on the basis of their extensive experience.

The proposed testimony of Drs. Lembke, Keyes and Gruber is grounded in reliable science, applies reliable methodology, will assist the trier of fact, and should not be excluded.

LEGAL STANDARDS

The legal standards applicable to this motion are set forth in Plaintiffs' *Daubert* Roadmap Brief, to which the Court is respectfully referred.

Of particular relevance on this motion, Plaintiffs note that the Supreme Court in *Daubert* was careful to emphasize that it is the expert's methodology, not his conclusion, that is the subject of the Rule 702 inquiry. Noting that the "overarching subject" of the Rule 702 inquiry "is the scientific validity and thus the evidentiary relevance and reliability - of the *principles that underlie* a proposed submission," *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594-95 (1993) (emphasis added), the Court went on to hold: "The focus, of course, must be solely on principles and methodology, not on the conclusions that they generate." *Id.* at 595. The Sixth Circuit has repeatedly echoed this caution. *Ky. Speedway, LLC v. Nat'l Ass'n of Stock Car Auto Racing, Inc.*, 588 F.3d 908, 915 (6th Cir. 2009); *Best v. Lowe's Home Ctrs., Inc.*, 563 F.3d 171, 177 (6th Cir. 2009); *United States v.*

Demjanjuk, 367 F.3d 623 (6th Cir. 2004). Nothing in Rule 702 or *Daubert* and its progeny, or in the rulings of the Sixth Circuit permits this Court to subject an expert's conclusions, as opposed to his methodology, to the *Daubert* analysis.²

Moreover, courts recognize that it is unreasonable to require the subject of scientific testimony to be “known” to a certainty, since science is an evolving process, and there are no certainties in science. *Daubert*, 509 U.S. at 590. The Supreme Court has recognized that there is a “range where experts might reasonably differ, and where the jury must decide among the conflicting views of different experts” See *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 153 (1999). The Sixth Circuit agrees and has elaborated:

‘Scientific knowledge’ establishes the standard of evidentiary reliability, and to be considered appropriately scientific, the expert need not testify to what is ‘known’ to a certainty but must only state an inference or assertion derived by the scientific method. Testimony meets this threshold when an expert, whether basing testimony on professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice in the relevant field.

Jahn v. Equine Servs., PSC, 233 F.3d 382, 388 (6th Cir. 2000) (citations and internal quotation marks omitted); see also *United States v. Bonds*, 12 F.3d 540, 561 (6th Cir. 1994) (“Absolute certainty of result or unanimity of scientific opinion is not required for admissibility so long as the conclusions drawn by the experts are based on generally accepted and *reliable* scientific principles”) (citation and internal quotation marks omitted).

² Although the Supreme Court spoke in terms of determining the reliability of a “theory or technique,” it is clear from the authorities cited in the text that the “theory” it was referring to was that underlying the particular methodology used, not the conclusion. Thus, the “theory” that is the subject of the *Daubert* inquiry on this motion is the methodology underlying the various studies discussed below (the reliability of which Defendants do not challenge) and the methodology of undertaking a review of scientific literature (which Defendants also do not challenge).

ARGUMENT

I. **DRS. LEMBKE AND KEYES APPLIED A RELIABLE METHODOLOGY TO OPINE THAT PRESCRIPTION OPIOIDS ARE A GATEWAY TO MISUSE OF, AND ADDICTION TO, BOTH PRESCRIPTION OPIOIDS AND ILLICIT DRUGS**³

Plaintiffs' expert Anna Lembke, M.D. is Chief of the Addiction Medicine Dual Diagnosis Clinic, Medical Director of Addiction Medicine, and Program Director of the Addiction Medicine Fellowship, in the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine. She is Board-certified in psychiatry and neurology, and in addiction medicine. She regularly treats patients with addiction to opioids and other substances; for the last 15 years, her clinical practice has included a significant proportion of patients taking prescription opioids for pain relief, for whom such drugs have resulted in misuse, dependence, and addiction.

Dr. Katherine Keyes is an Associate Professor of Epidemiology at Columbia University, specializing in substance use and substance use disorders epidemiology.⁴ Epidemiology is the “science of understanding the causes and distributions of population health” and “epidemiologists examine the dynamic nature of populations and how health and disease arises within them.”⁵ By definition, epidemiology plays a role in describing the opioid epidemic and its causes, and Dr. Keyes is, accordingly, qualified to opine on this topic. In addition, Dr. Keyes has extensive expertise on opioid-related harm, including large scale survey data and vital statistics analyses, as well as the development of theories, hypotheses, and published findings concerning the role of macro-social factors in producing the opioid epidemic.⁶ She has published 19 peer-reviewed journal articles on opioid use and related harms (and many more on drug use disorders generally), detailing trends over time in prescription opioid misuse, birth cohort trends in nonmedical opioid use and overdose, risk

³ Because Dr. Lembke and Dr. Keyes analyzed medical and epidemiological evidence, while Prof. Gruber made a causal assessment using the techniques of Health Economics, Plaintiffs discuss the reliability of Prof. Gruber's analysis separately from the reliability of that of Drs. Lembke and Keyes.

⁴ Report of Katherine Keyes, Dkt # 2000-9, at 1.

⁵ *Id.* at 7.

⁶ *Id.* at 2.

factors for non-medical prescription opioid use, and consequences of use across developmental periods, including consequences related to overdose.⁷

Drs. Lembke and Keyes applied their scientific training, expertise, and experience specific to the opioid crisis to formulate their opinions about the Gateway Effect. Defendants repeatedly refer to this as a “hypothesis,” but as discussed above, it not necessary that the Gateway Effect be proven to a certainty, or that it be generally accepted (although in fact it is) in order for it to be admissible. All that is required is that it Drs. Lembke and Keyes applied a reliable methodology and that their conclusion rests on a sound body of scientific evidence. This standard is readily met.

A. Drs. Lembke and Keyes Relied on a Substantial Body of Scientific Evidence in Reaching Their Conclusions about the Gateway Effect

Drs. Lembke and Keyes concluded that prescription opioids are a “gateway” to the use of illicit opioids based on extensive review of scientific and epidemiological literature. The literature they relied on is extensive, methodologically-sound, and peer-reviewed. Each of these experts has the requisite scientific background to read and analyze the relevant studies.⁸

The review of scientific literature is a sound methodology. *In re Gadolinium-Based Contrast Agents Prods. Liab. Litig.*, No. 1:08 GD 50000, 2010 WL 1796334, *mod. on recon.*, 2010 WL 5173568, *aff’d sub nom. Decker v. GE Healthcare Inc.*, 770 F.3d 378 (6th Cir. 2014) (finding expert testimony based on review of scientific literature admissible); *see also In re Heparin Prods. Liab. Litig.*, 803 F. Supp. 2d 712, 738 (N.D. Ohio 2011) (“Courts have admitted expert testimony as reliable where experts extrapolate their opinions from their knowledge and experience combined with a review of the relevant scientific literature.”); *Ferguson v. Lear Siegler Servs., Inc.*, No. 1:09CV635-MHT, 2012 WL 1058983, at *5 (M.D. Ala. Mar. 28, 2012) (finding the evidence the expert relied on in reaching his

⁷ *Id.* at 2.

⁸ Defendants suggest that Dr. Lembke and Dr. Keyes did not really conclude that the Gateway Effect is causal, pointing to occasional statements that certain data are “consistent” with causation (Def. Brief at 12, 14). This argument completely ignores the numerous occasions when Plaintiffs’ experts stated in their reports or at depositions that the prescription opioid epidemic *caused* the increased use of heroin/fentanyl.

conclusion (a combination of peer-reviewed articles and experimentation conducted by others) is reliable and he applied it in a manner consistent with scientific principles); *Tressler v. BNSF Ry. Co.*, No. CV-10-188-RMP, 2012 WL 315402, at *6 (E.D. Wash. Feb. 1, 2012) (finding medical and scientific literature review and evaluation of available epidemiological data is reliable methodology); *In re Avandia Mktg., Sales Practices & Prods. Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576, at *9 (E.D. Pa. Jan. 4, 2011) (“[The expert’s] opinions expressed in this case are based on reliable scientific methodology (the review of peer-reviewed, published studies and data using well established statistical and scientific principles).”).

That there are purportedly contrary conclusions set forth in competing epidemiological studies provides *no basis* to exclude opinions formed through the reasonable and reliable methodology followed by Plaintiffs’ experts. *See, e.g., Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 433 (7th Cir. 2013) (“Rule 702 did not require, or even permit, the district court to choose between those two studies at the gatekeeping stage. Both experts were entitled to present their views, and the merits and demerits of each study can be explored at trial.”).

Defendants contend that no reliable scientific evidence supports Dr. Lembke’s and Dr. Keyes’ conclusion. Although the focus of the *Daubert* inquiry is on methodology, and not on conclusions, in this case, a review of the substantial body of scientific evidenced on which Dr. Lembke and Dr. Keyes relied establishes the reliability of the methods and the admissibility of their conclusions.⁹

⁹ Defendants rely on *Huss v. Gayden*, 571 F.3d 442 (5th Cir. 2009), for the proposition that the underlying data relied on by Plaintiffs’ experts must explicitly state that “A causes B.” (Def’s. Br. Dkt. # 1857-1, at 7.) The circumstances were significantly different in *Huss*, and that case is not persuasive here. In *Huss*, Plaintiff’s expert relied mainly on a single study that included a warning that case-control designs do not prove causation between a drug and an injury. *Huss*, 571 F.3d at 458-459. Ordering a retrial, the Fifth Circuit advised the district court to hold a *Daubert* hearing to assess the reliability and relevance of the expert testimony. *Id.* Here, Plaintiffs’ experts relied on numerous authoritative texts and scientific literature that support the Gateway Effect, including reliable sources authored by Plaintiffs’ experts themselves prior to litigation. *See below*, Point I-B.

1. *Dr. Lembke's Opinions Are Supported by the Authoritative NASEM Report.*

An important piece of evidence Dr. Lembke considered in her analysis is the research and conclusions of a committee selected by the National Academies of Sciences, Engineering and Medicine (NASEM), to investigate and issue a report (the “NASEM Report”) on the opioid epidemic and responses to alleviate its effects. The Committee that issued that consensus report included Mark Schumacher, M.D., one of Plaintiffs’ experts.¹⁰ The NASEM Report, released in 2017, endorsed the validity of the Gateway Effect, as documented in the following excerpts: “A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a *gateway to increased heroin use*. ... [T]he interrelated nature of the prescription and illicit opioid epidemics means that one cannot be addressed separately from the other.”¹¹ “Another critical feature of the opioid crisis is that *the prescription and illicit opiate epidemics are intertwined*; indeed, a majority of heroin users report that their *opioid misuse or OUD began with prescription opioids*.”¹² “A number of studies have yielded evidence strongly supporting the conclusion that *the recent prescription opioid epidemic has resulted in a significant increase in domestic heroin use and associated overdose deaths*.”¹³ Finally, the NASEM Report stated that “a major concern is how prescription opioids contributed to this problem both by serving as ‘*gateway*’ *drugs to heroin use*,” and by ‘squeezing the balloon,’ through focused efforts to reduce their misuse (e.g., by development of ADFs [abuse-deterrent formulations]) leading to illicit sources and drugs such as heroin.”¹⁴ Dr. Lembke’s reliance on the NASEM Report supports the appropriateness of her conclusions..¹⁵

¹⁰ Ex. 1, Nat’l Acads. of Scis., Eng’g & Med. (NASEM), *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use* (The Nat’l Acads. Press 2017); see Biographical Sketches of Committee Members and Consultants 435 *et seq.*, identifying Plaintiffs’ expert, Mark Schumacher, M.D., as one of 18 renowned scientists and physicians selected to serve on the Committee that authored the 2017 NASEM report, which represents a consensus of the full Committee.

¹¹ *Id.* at 215, 248 (emphasis added); quoted in Report of Anna Lembke, MD, Dkt. #2000-10, ¶C.12.a, at 84-85.

¹² Ex. 1, NASEM Report, *supra* note 10, at 6 (emphasis added).

¹³ *Id.* at 207 (emphasis added, citations omitted).

¹⁴ *Id.* at 208 (emphasis added; citations omitted).

¹⁵ See Lembke Rep., Dkt. #2000-10, ¶ C. 12. a., at 84-85, quoting the NASEM report endorsement of the Gateway Effect; Report of Professor Jonathan Gruber, Dkt. #2000-6 at 18-19, citing NASEM Report conclusion that the

2. *Dr. Lembke's and Dr. Keyes' Research Included Review of Numerous Scientific Articles that Support the Gateway Effect.*

The scientific evidence relied upon by Plaintiffs' experts shows widespread acceptance of the role of both medical and non-medical use of prescription opioids in creating the epidemic of prescription opioid and illicit opiate abuse and mortality.¹⁶ Defendants' argue Dr. Lembke and Dr. Keyes considered only studies of non-medical use, but as described below, this is a false account of the data upon which they relied to support opinions that both medical and non-medical use of prescription opioids lead to use of illicit drugs. Rather, the studies Drs. Lembke and Keyes considered included studies involving both medical and non-medical use of prescription opioids. Most ludicrous, and offensive, is Defendants' complaint that Plaintiffs' experts do not rely on any "controlled clinical trial" (Defs. Br. Dkt. # 1857-1, at 9), as if one could ethically design a trial to expose one group to addictive drugs, and compare them to an unexposed group, to see whether more of the exposed group transitioned to heroin use, or for that matter, how many of the exposed group died of their exposure.

The studies on which Dr. Lembke and Keyes relied, and which support their opinions concerning the Gateway Effect, include:

- (a) Inciardi (2009); Lankenau (2012); Mars (2014); Siegal (2003)

A series of studies of heroin users, by different authors and in different environments (including Ohio), all found that prescription opioids were an initial step in the transition to heroin. A study of heroin users in Wilmington, Delaware, found that "most reported that prescription opioids

National Survey of Drug Use and Health (NSDUH) underestimates the extent of the epidemic of opioids and illicit drugs.

¹⁶ Defendants mistakenly argue that the Gateway Effect depends on a direct transition from "medical" use (as prescribed by a doctor) to heroin/fentanyl. Real life is not that black and white. While some of the literature summarized herein does fit that mold, other research shows that "medical" use can *follow* non-medical use of prescription opioids, and that the two may be intertwined, prior to use of heroin/fentanyl. Similarly, the overprescribing and excessive sale of opioids created the supply of non-medically used drugs that also provided another gateway to heroin/fentanyl, as documented in the literature.

were indeed their *gateway to heroin use*.”¹⁷ A study of young injection drug users in New York City and Los Angeles stated, “Initiation into prescription opioid misuse was facilitated by *easy access to opioids via participant’s own prescription*, family or friends, and occurred earlier than misuse of other illicit drugs. . . . *Prescription opioid misuse was a key feature of trajectories into injection drug use and/or heroin use . . .*.”¹⁸ A research paper evaluated transitions from opioid pills to heroin injecting in Philadelphia and San Francisco, and concluded: “Unlike those substances previously labeled ‘gateway drugs,’ *opioid pills seem to have a direct relationship with progression to heroin initiation*.”¹⁹ In Ohio, a 2003 investigation of recently initiated heroin users by the Ohio Substance Abuse Monitoring Network, found that 5 out of 10 subjects had used prescription opioids before initiating heroin use. The views of the authors are evident in the title: “*Probable Relationship between Prescription Opioid Abuse and Heroin Use*.”²⁰

In her Report, Dr. Keyes relied, in part, on the studies summarized above, among others, to opine that “prescription opioid use is *causally related* to heroin use.”²¹ Dr. Keyes also cited published data that “show[ed] that approximately 70-80 % of individuals who use[d] heroin in the last 20 years started their opioid use with prescription opioids.”²² Dr. Keyes found that “the high-quality evidence across reviews indicates that the risk of incident opioid use disorders, as well as recurrence of opioid use disorders, increase in a dose-response fashion with the dose of opioids and the length of opioid use, even after controlling for individual-level predisposing factors.”²³ Dr. Keyes applied a reliable

¹⁷ Ex. 2, J. Inciardi, *et al.*, *Prescription Opioid Abuse and Diversion in an Urban Community: The Results of an Ultra-Rapid Assessment*, *Pain Medicine* 10:537-548, 547 (2009); Keyes Rep., Dkt. # 2000-9, References #90.

¹⁸ Ex. 3, S. Lankenau, *Initiation Into Prescription Opioid Misuse Amongst Young Injection Drug Users*, *Int’l J. of Drug Pol’y*, 23:37-44, 34 (2012); cited in Lembke Rep., Dkt. # 2000-10, ¶ C. 12.e; Keyes Rep., Dkt. #2000-9, Reference #89.

¹⁹ Ex. 4, S. Mars, *et al.*, “Every ‘Never’ I Said Came True”: *Transitions from Opioid Pills to Heroin Injecting*, *Int’l J. of Drug Pol’y*, 25:257-266, 264 (2014); Keyes Rep., Dkt. # 2000-9, References #95.

²⁰ Ex. 5, H. Siegal, *et al.*, *Probable Relationship Between Opioid Abuse and Heroin Use*, *A. Fam. Physician* 67:942-945, 942 (2003) (emphasis added).

²¹ Keyes Rep., Dkt. # 2000-9, at 25 (emphasis added).

²² *Id.* at 26.

²³ *Id.* at 16.

methodology by relying on scientific studies supporting her opinion that use of opioids as prescribed can, and does, lead to opioid use disorders, including nonmedical opioid use, and heroin/fentanyl use.

(b) McCabe (2011, 2017, 2018)

Dr. Lembke's report includes the following: "McCabe *et al.* conducted a prospective national study of high school seniors in the U.S. to identify the sequence of medical versus non-medical use of prescription opioids, and the later development of a substance use disorder (addiction). They found that almost one in every two high school seniors who reported the *medical use* of prescription opioids after initiating NMUPO [non-medical use of prescription opioids] had two or more substance use disorder (addiction) symptoms at age 35.²⁴ These data show that teens exposed to prescription opioids without a prescription will often be further exposed through a subsequent medical prescription, and as a result are at increased risk of developing an opioid addiction later in life. The cumulative effect of prescription opioid exposure, through both medical and non-medical use, causally leads to opioid addiction."²⁵ In this study, medical use was found to contribute to substance use disorder, even when such use was preceded by non-medical use. The sequence does not diminish the importance of medical use as a gateway to further substance use disorders, and the over-supply created by Defendants' collective conduct was causally related to increased heroin/fentanyl use following either use of opioids as prescribed, or non-medical use, or both.

Two earlier studies by McCabe, applying the same methodology, provide further support for the Gateway Effect. In 2011, McCabe reported that, among adolescents who received medically-

²⁴ Ex. 6, S. McCabe, *et al.*, *A Prospective Study of Nonmedical Use of Prescription Opioids During Adolescence and Subsequent Substance Use Disorder Symptoms in Early Midlife*, Drug Alcohol Dependency (2019), at 379, doi:10.1016/j.drugalcdep.2018.10.027.

²⁵ *Id.* at 381; see also Lembke Rep., Dkt. # 2000-10, at 38-39, quoting from Ex. 7, Boyd, *et al.*, *Medical and Nonmedical Use of Prescription Pain Medication by Youth in a Detroit-area Public School District*, Drug Alcohol Dependency (2006), at 7, doi:10.1016/j.drugalcdep.2005.05.017 (observing an 8-fold increase in lifetime nonmedical use among students who had either current or previous prescriptions for pain medications).

prescribed pain medications in the past year, 20.1% reported misuse of those medications.²⁶ In 2017, McCabe found, “Adolescents who reported both medical and nonmedical use of prescription opioids were *more likely to indicate medical use of prescription opioids before initiating nonmedical use*,”²⁷ and that “this pattern may be driven by the one-third of adolescents who report NUPO [*nonmedical use of prescription opioids*] involving medications from their own previous prescriptions.”²⁸ McCabe’s conclusions provide especially relevant support for the Gateway Effect and the problems it engenders: “The findings provide *compelling evidence that medical use of prescription opioids and NUPO are highly correlated, especially among adolescents. . . . We found that the majority of NUPO involved a history of medical use, and this finding should provide some concern to health professionals who prescribe opioid medications to adolescents, given the serious health consequences associated with NUPO.*”²⁹ Most significantly, McCabe’s references supporting this last point include the Compton (2016) study³⁰ relied upon so heavily, but incorrectly, by Defendants to support the false premise that only nonmedical users are at risk. As McCabe warns, the *medical users of prescribed opioids become the nonmedical users of those same addictive drugs, who then become part of the population of heroin users described in the Compton article*. This is the Gateway Effect, in no uncertain terms.

(c) Edlund (2014)

A 2014 study by Edlund, *et al.*,³¹ used claims data from a healthcare database for patients who had been prescribed opioids by their doctors, for various acute and chronic conditions—

²⁶ Ex. 8, S. McCabe, *et al.*, *Medical Misuse of Controlled Medications Among Adolescents*. Archives of Pediatrics and Adolescent Medicine, August: a65(8): 729-735, 733 (2011). doi: 10.1001/archpediatrics.2011.114. “Misuse” included “taking too much, intentionally getting high, or using to increase alcohol or other drug effects.” *Id.* at 729.

²⁷ Ex. 9, S. McCabe, *et al.*, *Trends in Medical and Nonmedical Use of Prescription Opioids Among U.S. Adolescents: 1976-2015*. Pediatrics 139, Number 4 (2017), at 1. doi:10.1542/peds.2016-2387.

²⁸ *Id.* at 4-5.

²⁹ *Id.* at 7-8.

³⁰ See *id.* reference #40, at 9.

³¹ Ex. 10, M. Edlund, *et al.*, *The Role of Opioid Prescription in Incident Opioid Abuse and Dependence Among Individuals with Chronic Noncancer Pain*. Clin. J. Pain, 30(7):557-564 (2014). All of these results were highly statistically significant. See Lembke Rep., Dkt. # 2000-10 at 11, 15; Keyes Rep., Dkt. # 2000-9 at 15.

precisely the population who would not be at risk of addiction if Defendants' claims were true. Significantly, Edlund applied an "incidence" methodology, which assured that patients had neither recent opioid prescriptions nor OUD diagnoses prior to the start of the study; thus, the observed effects were most certainly due to the new onset of OUD, rather than any pre-existing condition. Edlund found that for low-dose (1-36 MME/day) chronic exposure (> 90days) to prescribed opioids, the odds ratio [OR] of developing OUD compared to those who were not prescribed opioids was 14.92; for medium dose (36-120 MME/day) chronic exposure, the OR was 28.69; and for high dose (>120MME/day) chronic exposure, the OR was 122.45.³² As noted by Dr. Lembke, these data show that both higher dose and longer duration of exposure to medically prescribed opioids increase the risk of OUD; when both higher dose and longer duration are in effect, patients are 122 times more likely to suffer OUD than patients who were not prescribed opioids.³³ By definition, patients with OUD are using their prescription opioids "non-medically;" the references relied on by Defendants acknowledge both a "clear link" between nonmedical use of prescription opioids and heroin use,³⁴ and that "[t]he transition from nonmedical use of prescription opioids to heroin use appears to be part of the progression of addiction in a subset of nonmedical users of prescription opioids"³⁵ As shown by Edlund, patients who receive properly prescribed opioids become an ongoing source of non-medical users who provide a feeder population for illicit drug use. Finally, Edlund's study provides all the major hallmarks of causality between exposure to prescription opioids and OUD.³⁶

³² *Id.* at 561.

³³ Lembke Rep., Dkt. # 2000-10, ¶ C. 3.a. iv., at 15.

³⁴ See, e.g., Ex. 11, W. Compton, *et al.*, *Relationship Between Nonmedical Prescription Opioid Use and Heroin Use*, N. Engl. J. Med., 374-154-63, at 157 (2016).

³⁵ *Id.* at 160.

³⁶ See Ex. 12, Reference Manual on Scientific Evidence (3d. 2011), at 597-608: Defendants misleadingly quote only the sentence regarding researchers calling for "stronger evidence" to reach a conclusion of causality, without mentioning that the Reference Manual then goes on to identify the factors that are used by epidemiologists, and accepted by the courts, in reaching such conclusions of causality. Evidence in this case satisfies those factors: Temporality (increased heroin use followed increased prescription opioid exposure); strong association between prescription opioid exposure

(d) Other Studies

Boscarino evaluated opioid use disorder among a random sample of Pennsylvania outpatient clinic patients who had five or more opioid drug prescriptions for chronic, non-cancer conditions in a 12 month period. Boscarino reported that over 41% of the subjects met DSM-5 criteria for OUD, ranging from mild (approximately 28%) to moderate (approximately 9%) to severe conditions (approximately 4%).³⁷ These were normal patients in a normal clinic receiving legitimate medical prescriptions, who nevertheless became non-medical users susceptible to heroin/fentanyl abuse.

The Davis study, published in 2008, found: “The scientific literature has identified several specific sub-populations involved in PO [prescription opioid] misuse and diversion that are so diverse that it is not feasible to study them in a single investigation—e.g., high-school students, college students, older persons, and women, *most of whom initially obtain POs via legitimate medical practices.*”³⁸

A very recent peer-reviewed publication evaluated prescriptions and diagnoses among enrollees in both Medicaid and commercial databases. This study found that “[m]ost enrollees with OUD in the data had current opioid prescriptions,”³⁹ providing further confirmation that opioids prescribed by a doctor offer no protection against OUD, but instead are closely linked to, and inseparable from, such diagnoses. The progression from medical prescription to opioid misuse, and

and OUD (OR as high as 122 for chronic high dose exposure, far greater than the relative risk of 10, said to be “extremely difficult to imagine any bias or confounding factor that might account for it,” dose-response relationship (the greater the exposure, the greater the risk of disease); replication of results (Edlund study itself affirms dose-response relationship seen in other studies); alternative explanations considered (OR of over 10 makes bias and confounding extremely unlikely); consistency with other knowledge, i.e., it is well-known that prescription opioids are analogs of heroin and highly addictive.

³⁷ Ex. 13, J. Boscarino, *et al.*, *Opioid-Use Disorder Among Patients on Long-Term Opioid Therapy: Impact of Final DSM-5 Diagnostic Criteria on Prevalence and Correlates*, Substance Abuse Rehabilitation, (2015), at 83. doi:10.2147/SAR.S85667, cited in Lembke Rep., Dkt. # 2000-10 ¶ 5.f, at 47-48; cited in Keyes Rep., Dkt. # 2000-9, at 15-16.

³⁸ Ex. 14, W. Davis, *Prescription Opioid Use, Misuse, and Diversion Among Street Drug Users in New York City*, Drug and Alcohol Dependence, 92:267-276, at 268 (2008) (emphasis added; internal references omitted); Lembke Rep., Dkt. # 2000-10 Exhibit B, List of Materials Considered, #88, at 7.

³⁹ Ex. 15, M. Ali, *et al.*, *Opioid Use Disorder and Prescribed Opioid Regimens: Evidence from Commercial and Medicaid Claims, 2005-2015*, J. Med. Toxicology, Jul;15(3):156-168, at 156 (2019). doi: 10.1007/s13181-019-00715-0.

then to heroin, is documented in the scientific literature as a gateway sequence that Defendants omit from their arguments.

A recent, 2018 study found: “The *majority* of US high school seniors with both medical use and nonmedical use of prescription opioids *reported medical use before initiating nonmedical use of prescription opioids*, suggesting a role of leftover prescriptions in the transition to a nonmedical use of prescription opioids. This may be due, in part, to the perception that prescription opioids are safe if they are prescribed by physicians *despite the fact that the addiction potential is similar to heroin*.”⁴⁰

Additional recent studies demonstrate that even short-term, “proper” use of prescription opioids leads to prolonged use of the drugs, long after the acute episode has subsided, and that higher short-term exposure leads to much higher rates of long-term use unrelated to the initiating event. *See, e.g.*, Brummett, et al., (new, persistent use of opioids by 5.9-6.5% of minor and major surgery patients, compared to 0.4% in a non-operative control cohort;⁴¹) and Delgado (opioid prescriptions of > 225 milligrams morphine equivalent following acute ankle sprain were associated with approximately 5 times higher rates of prolonged use than those with lower or no exposure).⁴² These articles are cited in Dr. Lembke’s Report, supporting her opinions that so-called “proper” medical use can and does lead to OUD and long-term dependence on these addictive drugs, and that a doctor’s prescription does not provide immunity from addiction.⁴³

3. *Dr. Lembke and Dr. Keyes Used Appropriate Methodology to Conclude that the Same Studies that Link Prescription Opioid Use to Illicit Opioids Applies to Fentanyl*

Much of the research linking prescription opioid exposure to illicit opiates was based on data that preceded the spike in illicit fentanyl use, and thus the studies generally refer to heroin as the

⁴⁰ Ex. 16, C. Harbaugh, *Persistent Opioid Use Among Pediatric Patients After Surgery*, Pediatrics 141(1), at 5 (2018)(emphasis added).

⁴¹ Ex. 17, C. Brummett, et al., *New Persistent Opioid use After Minor and Major Surgical Procedures in U.S. Adults*. JAMA Surgery, at 1 (2017); Lembke Rep., Dkt. 2000-10 at 71.

⁴² Ex. 18, M. Delgado, *Nat’l Variation in Opioid Prescribing and Risk of Prolonged Use for Opioid-Naïve Patients Treated in the Emergency Department for Ankle Sprains*, Annals of Emergency Med., 72:389-400, at 389 (2018).

⁴³ Lembke Rep., Dkt. # 2000-10 at 71.

target illicit drug following prescription opioids.⁴⁴ Dr. Lembke and Dr. Keyes properly concluded, however, that the same pathway would apply to illicit fentanyl. Part of the reason for this is that heroin use necessarily exposes patients to fentanyl as well, due to the widespread fentanyl contamination of the heroin supply. As noted by the CDC: fentanyl “is often mixed with heroin and/or cocaine as a combination product – with or without the user’s knowledge – to increase its euphoric effects.”⁴⁵ This conclusion is reinforced by the report of defense expert Heath Jolliff, D.O., who states that “in 2017 nearly 50% of confiscated heroin contained a synthetic opioid (e.g. fentanyl, carfentanil) and in 2018 that number rose to nearly 70%. In short, users of heroin in Ohio and the doctors who treat them expect that they are being regularly exposed to fentanyl.”⁴⁶

Therefore, the same sources cited by Plaintiffs’ experts as evidence of the Gateway Effect of prescription opioids apply equally to both heroin and fentanyl, and Drs. Lembke and Keyes properly relied on these sources for their conclusions with respect to both heroin and fentanyl.

4. *Testimony of CDC Officials Substantiates the Progression from Medical Use to Nonmedical Use of Prescription Opioids, and to Illicit Opiates.*

The Federal Response to the Opioid Crisis (2017) included testimony from Centers for Disease Control and Prevention officials, providing additional support for the Gateway Effect. On October 5, 2017 Deb Houry, MD, MPH, Director, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, HHS, testified before the US Senate Health, Education, Labor and Pensions Committee, as follows: “To reduce the rate of new opioid addiction, we need to decrease overall exposure to opioids. For many people, *that first prescription will be for an immediate release (IR) formulation of the drug. Some people will go on to become addicted and abuse long-acting formulations that can deliver higher doses, especially when manipulated. Some of these people will*

⁴⁴ See, e.g., Ex. 19, P. Muhuri, *et al.*, *Ass’n of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States*, CBHSQ Data Rev., 1-16 (August 2013).

⁴⁵ Ex. 20, Ctrs. for Disease Control and Prevention, *Fentanyl*, <http://www.cdc.gov/drugoverdose/opioids/fentanyl.html>.

⁴⁶ Ex. 21, Report of Heath A. Jolliff, DO, at 33.

*eventually move onto street drugs, such as heroin, which are increasingly the low-cost alternative. We know that this route of addiction correlates with exposure. A certain percentage of patients exposed to opioids will go on to develop an addiction to the drugs. One approach to reducing the rate of new addiction, then, is to reduce exposure to prescription opioid drugs.”*⁴⁷

On October 25, 2017, Anne Schuchat, MD, Rear Admiral, US Public Health Service; Principal Deputy Director, Center for Disease Control and Prevention, HHS, testified before the US House Energy and Commerce Committee, as follows: “In fact, about 90 percent of all opioid prescriptions in the United States are written for IR formulations of these drugs. *IR opioid products serve as the gateway for patients and non-patients* who may continue to use or misuse these products, which could lead to new addiction.”⁴⁸

These views of high-ranking federal health officials with special knowledge of the opioid epidemic provide additional support for the validity of the Gateway Effect opinions of Plaintiffs’ experts.

B. The Opinions of Dr. Lembke and Dr. Keyes Are Further Supported by Their Own Pre-Litigation Research and Publications

The opinions of Drs. Lembke and Dr. Keyes are further supported by the fact that each of them conducted extensive research on this topic *before being retained as experts in this litigation* and each of them published their conclusions about the Gateway Effect.

In 2016 (before she had any connection to this litigation), Dr. Lembke published her influential book, *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard*

⁴⁷ Ex. 22, *The Federal Response to the Opioid Crisis before the S. Comm. On Health, Education, Labor and Pensions*, 115th Congr. 1-16 (2017) (statement of Deb Houry, MD, MPH, Director, National Center for Injury Prevention and Control, CDC, HHS), at 14 (emphasis added), <https://www.cdc.gov/washington/testimony/2017/t20171005.htm>.

⁴⁸ Ex. 23, *Federal Effort to Combat the Opioid Crisis: A Status Update on CARA and Other Initiatives before the H. Comm. On Energy and Commerce*, 115th Congr. (2017), at 15 (statement of Anne Schuchat, MD, Rear Admiral, U.S. Public Health Service; Principal Deputy Director, CDC, HHS) (emphasis added) <https://www.cdc.gov/washington/testimony/2017/t20171025.htm>.

to Stop.⁴⁹ That publication included numerous references to the literature demonstrating the causal link between prescription opioids and heroin, in a chapter entitled, “Prescription Drugs as the New Gateway to Addiction,” with subchapters such as “Vicodin—A Gateway Drug,” “Heroin—the New Vicodin,” and “The Gateway Now a Runway.”⁵⁰ Dr. Lembke’s book cited peer-reviewed studies supporting her conclusion that “many people with no addiction history can become addicted to opioid painkillers in the course of routine medical treatment,” such as long-term opioids for low back pain; opining there, as here, that “[f]or increasing numbers of people, especially young people, *prescription drugs are the first exposure to addictive substances and the first stepping stone to future addictive use.*”⁵¹ Dr. Lembke’s book then provided an illustrative example of the Gateway Effect, from among her thousands of patients, recounting the history of a young man who was first exposed to opioids during treatment for removal of wisdom teeth, became addicted to Vicodin prescribed for the post-removal period, and went through a series of addictive pharmaceuticals until finally becoming hooked on heroin.⁵²

Similarly, Dr. Keyes also published on the Gateway Effect before becoming involved in opioid litigation. Dr. Keyes’ pre-litigation, peer-reviewed publications focused on questions that are directly relevant to, and supportive of, the validity of the Gateway Effect. For example, in a study published in 2015, Dr. Keyes wrote, “*Legitimate opioid use by 12th grade significantly predicts future opioid*

⁴⁹ Ex. 24, Anna Lembke, M.D., *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop* (2016).

⁵⁰ *Id.* at 21-37.

⁵¹ *Id.* at 22-23 (emphasis added).

⁵² *Id.*; Ex. 25, Anna Lembke Dep. (04/24/19), Dkt. # 1966-2, at 14:16-15:3. A recent peer-reviewed study provides affirmation of this Gateway Effect example. Schroeder, *et al.*, reporting on a study of 14,888 persons aged 16 to 25 years-old who received an initial opioid prescription from a dentist, found that “6% were diagnosed with an opioid use disorder (OUD) within one year. For women in this group, the rate was 10%.” This study highlights the risk to teens and young adults, even after limited exposure to a dental procedure, such as removal of wisdom teeth.” (Lembke Rep., Dkt. # 2000-10, 40) *see, e.g.*, Ex. 26, A. Schroeder, *et al.*, *Ass’n of Opioid Prescriptions from Dental Clinicians for U.S. Adolescents and Young Adults with Subsequent Opioid Use and Abuse*, JAMA Internal Med (2018) Table 3, at E6, doi:10.1001/jamainternmed.2018.5419.

misuse after high school.”⁵³ Dr. Keyes also reported in a 2014 article: “Increased medical use of prescription opioids has resulted in increased access to opioids for nonmedical use, either through the nonmedical use of legitimately acquired prescriptions or through formal or informal distribution networks.... [t]he nonmedical prescription opioid use epidemic may portend future increases in illicit drug use as well, considering that *nonmedical prescription opioid users are more likely than are nonusers to transition to heroin and other illicit drugs.*”⁵⁴ These two excerpts support the Gateway Effect—that prescription opioid use leads to nonmedical use, and that nonmedical use leads to heroin and other illicit drugs—researched, peer-reviewed and published by Dr. Keyes, three years prior to beginning work in the opioid litigation.

Dr. Lembke’s and Dr. Keyes’ pre-litigation publications of their findings, which match their opinions in this case, provide further assurance of the reliability of their opinions. *See Johnson v. Manitowoc Boom Trucks, Inc.*, 484 F.3d 426, 434 (6th Cir. 2007) (“That an expert testifies based on research he has conducted independent of the litigation provides important, objective proof that the research comports with the dictates of good science”) (citation omitted); *Mike’s Train House, Inc. v. Lionel, L.L.C.*, 472 F.3d 398, 408 (6th Cir. 2006); *Nelson v. Tenn. Gas Pipeline Co.*, 243 F.3d 244, 252 (6th Cir. 2001); *see also Kumho*, 526 U.S. at 152 (purpose of gatekeeper role is to ensure that expert “employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field”). Defendants’ Motion ignores Dr. Lembke’s important research and

⁵³ Ex. 27, R. Miech, *et al.*, *Prescription Opioids in Adolescence and Future Opioid Misuse*, *Pediatrics*, Volume 136:e1169-1177 at e1173 (2015) (emphasis added). The Journal editors added the following comment to Dr. Keyes’ article, further supporting the validity of Gateway Effect: “Legitimate opioid is a risk factor for subsequent misuse of opioids among adults. This study provides the first population-based estimate of the risk of future opioid misuse associated with legitimate opioid use among adolescents.” *Id.* at e1169. In the context of the opioid epidemic, Plaintiffs use and understand the term “legitimate” to mean only that the user took a drug prescribed by a doctor, in accordance with instructions. The term should not be interpreted to confer “legitimacy” on the enterprise of vastly overprescribing opioids based on false and misleading representations regarding claimed benefits and purported absence of risk when taken pursuant to a doctor’s prescription.

⁵⁴ Ex. 28, Katherine Keyes, *et al.*, *Understanding the Rural–Urban Differences in Nonmedical Prescription Opioid Use and Abuse in the United States*. *A. J. Public Health*, 104:e52–e59, at e53 (2014), doi:10.2105/AJPH, 2013.301709 (emphasis added).

credentials on this issue.

C. Neither Defendants' Experts, nor the Articles Cited by Defendants Undermine the Reliability of Dr. Lembke's and Dr. Keyes' Opinions

Defendants rely on their own experts' differing interpretation of the studies discussed above to suggest that Plaintiffs' experts' opinions are unreliable. (Def. Brief at 10, 15-16). Plaintiffs can, and will, as readily take the opposite position in asserting that Drs. Lyerla and Rahilly-Tierney have misinterpreted or overlooked certain studies. Defendants also cite other literature they contend supports their contention that the Gateway Effect lacks scientific support, but, like the differing opinions of Defendants' experts, these articles do not undermine the reliability of Dr. Keyes's and Dr. Lembke's opinions. Disagreements about inferences to be drawn from the literature "should be admitted to aid the jury in deciding those issues." *Gadolinium*, 2010 WL1796334, at *4; *see also Schultz*, 721 F.3d at 433.

Moreover, the studies Defendants cite do not support their challenge to Dr. Lembke's and Dr. Keyes' opinions in any event.

1. The Compton Article Does Not Support the False Dichotomy Defendants Seek to Establish between Medical and Non-Medical Use of Prescription Opioids

The Defendants rely on a 2016 article by Compton to challenge the Gateway Effect, by emphasizing a false dichotomy between nonmedical and medical use, when in fact the literature establishes that these are intertwined and inseparable, as explained in the sources cited above. In this regard, it is noteworthy that Compton himself eschewed such dichotomies, stating: "Fundamentally, prescription opioids and heroin are each elements of a larger epidemic of opioid-related disorders and death. *Viewing them from a unified perspective is essential to improving public health.*"⁵⁵ Importantly, Compton's article is addressed only to the transition from nonmedical use to heroin; Compton provides no comment about the transition from medical to nonmedical use. The latter subject is

⁵⁵ Ex. 11, Compton, *NMPOU and Heroin Use*, *supra* note 34, at 161 (emphasis added).

addressed in the studies summarized above, which show that medical and non-medical use are intertwined, and that medical use frequently precedes and gives rise to nonmedical use.

The Compton article also supports the opinion of Dr. Keyes, criticized by Defendants, that prescription opioid users who transition to heroin can explain the majority of increases in heroin use in the US, although the proportion of opioid users who progress to heroin is relatively small. (Defs. Br. Dkt. # 1857-1, at 5, quoting Keyes Report at 8). Compton states: “Of note, given the large number of nonmedical users [of prescription opioids], *even a small percentage who initiate heroin use translates into several hundred thousand new heroin users.*”⁵⁶ This evidence, from an article relied upon by Defendants, shows that there is no contradiction between the relatively small proportion of prescription opioid users who transition to heroin, on the one hand, and the large absolute number of new heroin users, on the other. Again, Dr. Keyes has applied a reliable methodology by relying on peer-reviewed literature to support her opinions.

2. Defendants’ Brief Omits a Follow-Up Article by Gilson in 2017.

A particularly glaring example of Defendants’ selective use of the literature is found in their misleading reference to a 2014 review by Cuyahoga Medical Examiner, Thomas Gilson, MD, to support a claim that “there is a dearth of firm evidence establishing the role of OPR [opioid pain relievers] as a gateway to heroin.” (Defs. Br. Dkt. # 1857-1, at 5-6.) Defendants cite this article as an example of a supposed conflict between Plaintiffs’ litigation experts and the pre-litigation views of a non-retained witness. Defendants fail to inform the Court that Dr. Gilson published a follow-up article in 2017, which stated: “While this crisis appears to have its *roots in the overprescribing of opioid pain relievers (OPR)*, more recent years have seen *a transition to illicit drugs*, primarily heroin and fentanyl.”⁵⁷ The 2017 article is clearly supportive of the Gateway Effect. Defendants further claim that Dr.

⁵⁶ *Id.* at 158 (emphasis added).

⁵⁷ Ex. 29, T. Gilson, *et al. The Evolution of the Opiate/Opioid Crisis in Cuyahoga County*. Acad. Forensic Pathology, 7:41-49, at 42 (2017) (emphasis added).

Keyes did not review literature subsequent to the Compton 2016 article with regard to the Gateway Effect; even a cursory glance at her list of references shows this assertion to be false, and the Gilson 2017 article itself, referenced in Dr. Keyes' Report, is sufficient to refute their claim.⁵⁸

Of particular significance, a web page for a recorded interview with Dr. Gilson provides a link to a PowerPoint prepared by Lee Hoffer, Ph.D, MPE, Professor of Anthropology at Case Western Reserve University, titled "Modelling Local Heroin Markets."⁵⁹ The web page bears the statement: "These presentations are provided by Thomas Gilson, M.D. Medical Examiner of Cuyahoga County." A section of the PowerPoint bears the heading, "Heroin Markets & Heroin Trends," and a sub-heading, "What is different about the current trend in heroin use?" Answering this question, the slides state: "The problem: large populations of people are *addicted* and require access to opiates. Rx [prescription] opiate meds trends have exponentially increased the potential **demand** for heroin. *The outcome*: Many people who used Rx opiates (for pain or recreation) switched to heroin... **why? Rx Opiate users believe heroin & Rx opiate meds are the same thing...** **Making Rx opiates = heroin has made heroin more 'socially acceptable'.** ... Heroin is cheaper? (\$10 bag vs. \$25 pill *street*). Heroin is easier to acquire. 1. Heroin does not require a prescription, visiting a doctor, or access to a doctor. 2. Heroin has never been scarce. 3. The market is easy to access."⁶⁰ Professor Hoffer's presentation includes the compelling graphic representation of the Gateway Effect,⁶¹ shown below:

⁵⁸ See Keyes Rep., Dkt. # 2000-9, List of references, #74, the Gilson (2017) article.

⁵⁹ Like Plaintiffs' expert Dr. Schumacher, Professor Hoffer was a member of the prestigious Committee that prepared the NASEM 2017 Report on the opioid epidemic. See Ex. 1, NASEM Report, *supra* note 10, Biographical Sketches of Committee Members, at 440.

⁶⁰ Ex. 30, Greg McNeill, *Episode 7 – Dr. Tom Gilson*, Cover2 Resources Podcast: About the People, Places and Things Making a Difference in the Opioid Epidemic (June 16, 2016), <https://cover2.org/episode-7-dr-tom-gilson-cuyahoga-county-medical-examiner/>; and Ex. 31, Hoffer presentation link "provided by Thomas Gilson" at 19-25 (emphasis in original)(Lee Hoffer, Ph.D., MPE, *Modelling Local Heroin Markets*, https://cover2.org/wp-content/uploads/2016/04/Hoffer_Task-Force_2016.pdf).

⁶¹ Ex. 31, Hoffer Task Force, *supra* note 60, at 30.



Dr. Gilson's selection of Professor Hoffer's presentation for this web page is an implicit endorsement of Hoffer's view, which, in turn, strongly supports the Gateway Effect of transition from prescription opioids to heroin. Defendants' reliance on Dr. Gilson's earlier article is off target and misleading. In fact, Drs. Gilson and Hoffer strongly support the Gateway Effect.

II. PROFESSOR GRUBER APPLIED RELIABLE METHODS IN THE FIELD OF HEALTH ECONOMICS TO SUPPORT HIS OPINIONS THAT SHIPMENTS OF PRESCRIPTION OPIOIDS CAUSED ILLICIT OPIOID-RELATED HARMS.

As set forth in Dr. Jonathan Gruber's Expert Report and in Plaintiffs' opposition brief to Defendant's *Daubert* motion seeking exclusion of his testimony, Dr. Gruber is a prominent health economist from Massachusetts Institute of Technology who uses fundamental tools of economic analyses to conclude that greater shipments of prescription opioids led to greater opioid-related harms, including harms related to heroin and fentanyl abuse. *See generally* Pls' Opp. to Defs.' *Daubert* Mot. to Exclude the Ops. Offered by Jonathan Gruber, §§ I-III. Relevant to this motion, Dr.

Gruber relies upon epidemiological studies to support this opinion. *Id.* § II, D.

Contrary to Defendants’ assertions, Dr. Gruber explicitly considered possible alternative causes, such as economic opportunity, citing peer-reviewed literature showing that economic conditions “explain little of the increase in drug mortality in recent decades and that changes in the drug environment, including the availability of prescription opioids, instead account for nearly all of the increases in drug mortality.”⁶² Dr. Gruber’s deposition testimony supplies further support: “I did perform a number of analyses and considerations regarding to [sic] the third possibility that there’s an omitted factor causing both” increased shipments and increased mortality, including economic conditions, non-opioid mortality and demographic factors that could influence medical need for opioids.⁶³

Defendants cite an isolated deposition fragment referring to a set of five *epidemiological* studies, to argue that Dr. Gruber’s opinions as a whole “do not prove a causal relationship to the standards that we use in economics literature.”⁶⁴ (Defs. Br. Dkt. # 1857-1, at 14-15). This misleading argument ignores that Dr. Gruber, an economist, based his opinions concerning causation on standard methods in his field of health economics, including regression analysis, that he clearly and repeatedly testified *do meet standards of proving causation* of the transition from prescription opioids to heroin. Thus, Defendants omit Dr. Gruber’s response when asked whether “higher consumption in areas with higher shipments” was “a causal relationship,” to which he replied, “yes, it’s a *causal relationship*, yeah, that’s right.”⁶⁵ Dr. Gruber specifically testified, “we established a *causal relationship*, not just a correlation,” between growth in shipments and prescription overdose mortality up to 2010; that after 2010, “the *evidence is clear from the time period we present to make the causal case* that in those

⁶² Gruber Rep., Dkt. # 2000-6, ¶¶ 100-105, at 70-73.

⁶³ Ex. 32, Jonathan Gruber Dep. (04/25/19), Dkt. # 1962-15, at 127:20-130:18, 134:14-137:18.

⁶⁴ *Id.* at 332:1-334:6.

⁶⁵ *Id.* at 191:24-192:12.

counties with high shipments, that's where the illicit deaths went up the most;" and "we then, as is *standard empirical practice*, tried to rule out other factors that could explain that."⁶⁶

Even as to the five epidemiologic studies, Defendants omit Dr. Gruber's testimony that he considered them as "part of the body of evidence that shows the link between shipments of opioids and illicit opioid use."⁶⁷ In other words, Dr. Gruber's reliance of these epidemiological studies is simply one reason among several other empirical analyses utilized by Dr. Gruber to support his core opinion that illicit opioid related harms were a direct result of prescription opioid shipments. *See* Pls' Opp. to Defs.' *Daubert* Mot. to Exclude the Ops. Offered by Jonathan Gruber, § II.⁶⁸

CONCLUSION

For the foregoing reasons, this Court should deny Defendants' Motion in its entirety.

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Respectfully submitted,

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⁶⁶ *Id.* at 202:7-203:5; 207:16-208:4; 234:4-235:21 (emphasis added).

⁶⁷ *Id.* at 336:14-337:10.

⁶⁸ Plaintiffs note that although Defendants make much of the purported significance of "medical" versus "nonmedical" use of prescription opioids, that distinction is irrelevant to Dr. Gruber's opinion that higher prescription opioid shipments gave rise to increased mortality. Regardless of whether the prescription opioids were medically prescribed or diverted to "misuse," the outcome of Defendants' aggressive marketing and failure to monitor excessive sales was the same—a tragic epidemic of deaths in the bellwether counties and beyond.

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